opinion upon museum specimens, said that the spongy bone became dense bone, the lymphoid marrow became yellow marrow, and the synovial membrane disappeared. A series of skiagrams of knee joints which I have resected indicate that this is correct. I believe it to be a fact, but cannot prove it as yet. If it is, the whole rationale of the cure of a tuberculous joint becomes evident. We have learned that the disease exists only in the synovia and in the lymphoid marrow.[3] If these two tissues disappear, the disease will die out. It cannot exist where these two tissues are not. Hence all we need to do to cure tuberculosis in the joint is to destroy function, while avoiding secondary infection.

In the hip the destruction of the joint is accomplished in resections by producing a dislocation or an ankylosis. The impossibility of removing all the diseased tissue from the acetabulum is immediately apparent.

There is no essential difference between tuberculosis of the lungs and of the joints. Doubtless tuberculous foci may occur in the marrow of the bone ends, and may heal up without recognition during life, as they may in the lungs. The uncertainty of any absolutely permanent cure of pulmonary tuberculosis when once it has advanced to clinical recognition is well known. I believe the prospect of a permanent cure of joint tuberculosis in the adult, by conservative means is even poorer. Therefore our rules for treatment of tuberculosis in the adult are:

1. The treatment should always be radical, *as soon as the diagnosis is positively made.*

2. The object of the treatment should be to destroy function in the joint. If this be impossible, every particle of infected tissue must be removed at any cost.

3. Secondary infection should be sedulously avoided.

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1. Rosenow: Journal of the Infectious Diseases, 1913, XIV, 1 and 61.
2. I except one great type of joint disease from this categlory—Goldthwaite's hypertrophic arthritis, the English osteo-arthritis, the German "arthritis deformans."
3. The internal layer of the periosteum seems to partake of the function and reactions of the marrow in that part of the bone where it is located. It may be considered for our purposes as a layer of external marrow.

THE CURATIVE TREATMENT OF PNEUMONIA, WITH A REPORT ON THE USE OF LEUKOCYTIC EXTRACT.*

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Medical research thus far has not developed any means of specifically destroying the invading organisms of pneumonia. Our curative efforts must be limited to aiding the biologic mechanism of attack, defence, and reinforcement. First by putting the patient in a condition of physiologic rest we allow his body cells and fluids to concentrate on the development of his defence. No vital power should be diverted by muscular effort, mental excitement, or nervous fatigue. Nutrition should be as nourishing and as abundant as the patient can dispose of; light solid food when the digestive function is efficient, fluid when the conditions require it. All avenues of excretion must be clear and efficient. The skin, the kidneys and the bowels must be kept active, that waste products of an increased metabolism shall not accumulate to embarrass the defense.

For a successful fight against any infection the animal economy requires an abundance of fluid. I consider the ingestion of large quantities of water a *sine qua non* in the successful management of severe pneumonias. Administered in copious drafts by mouth and by Murphy drip proctoclysis an average adult should take from five to eight pints daily. Normal or twice normal saline may be given by the bowel. When given subcutaneously the use of Ringer's solution possesses distinct advantages in the calcium effect on the heart, a valuable suggestion from Dr. W. W. Kerr.

The maintenance of blood pressure in severely toxic cases I consider a part of a curative therapy. It is best attained by the injection of pituitrin as used by Solis-Cohen [1] at Jefferson Medical College Hospital.

Quinine in large doses in the early days of the disease has, I believe, a curative action on the infection and deserves recognition in a consideration of a rational therapy. In the same way oxygen is not only a symptomatic remedy but is a curative measure in two ways. It stimulates circulation and respiration and by altering the oxygen tension it tends to obviate the formation in the red cells of methemaglobin, sometimes a determining factor of a fatal issue.

Physicians have long hoped for a rational biologic treatment for pneumonia. Thus far however the mortality of the disease has not been affected. Indeed if recent massive statistics by G. A. Gibson [2] are to be believed, the death rate from pneumonia in hospitals is higher in the last decade than in the previous forty years.

Certain attempts have been made to make use of specific sera. Clough [3] of Baltimore has succeeded in protecting mice by the use of human serum but only against the homologous strain of pneumococcus. Indeed, the great barrier to the success of sera lies in their strictly specific limitation to the homologous strain. The great multiplicity of strain of the pneumococcus and its ready mutability seems to render the task impracticable. In 1904 Anders [4] reported on 535 cases treated with anti-pneumococcic serum, and concluded that the results did not warrant its general use. The fact that a serum that is potent to protect an animal from a subsequent inoculation is powerless to aid an animal when once the infection is under way further tends to discourage specific therapy. Still further, it has been shown that a certain concentration of antibody content in the body fluids, the Schwellenwert or threshold concentration of Neufeld and Ungermann [5] is necessary for results even in animal work, a concentration which seems beyond the practical limits of serum administration.

Dochez [6] has apparently made progress in serum

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therapy of pneumococcus pneumonia by the classification of the cases into four groups, each of which is caused by a subfamily of strains, each strain of a given subfamily agglutinable with a serum specific for the corresponding group. Rufus Cole [7] has reported his clinical experience with twenty cases after the method of Dochez, and is much encouraged by his results. The agglutination of the causative germ in a given case by the serum to be used in the treatment, places his method on a rational foundation.

Vaccine therapy has not produced results clinically because of the time requirements.

Rosenow and Hektoen [8] have worked with partly autolyzed pneumococci. Rosenow has shown that when pneumococci are suspended in salt solution the toxic substances or "virulin" pass into solution while the residue has well marked antigenic properties and no toxic effect. Working with these antigens, the authors have published very persuasive clinical results.

One other biologic method remains and it is with this that my report is chiefly concerned. The rationale of the leukocytic extract of Hiss and Zinsser lies in the antagonism to bacterial toxins, of the endoferment of the phagocytic cell rendered available by maceration in sterile water. The phagocytic cell is able to protect itself against the digestive action of the ingested bacterium by virtue of the digestive ferment contained within itself. This so-called ferment termed by Hiss an endoantitoxin, is set free by cytolysis in sterile water, and remains in solution in the same way as the toxins of the pneumococcus pass into solution in saline in the method of Rosenow and Hektoen. Working with this extract of rabbit's leukocytes, Hiss and Zinsser [9] demonstrated by very clear-cut results the effect of the extract in saving animals injected with virulent pneumococcus cultures, the injected animals recovering with considerable regularity, the control animals uniformly dying.

Mr. Arthur Meinhard has but recently completed elaborate experiments on rabbits, the results of which are herewith published. He has amply verified the findings of Hiss and Zinsser. The latter authors [10] were able to study the effect of the extracts clinically and obtained very promising results in a number of infections, some of the cases being pneumonia. Lambert [11] treated a number of cases of various infections and reported results which in his opinion warranted further trials of the remedy.

Floyd and Lucas [12] employed the remedy in forty cases in 1909 with a mortality of 12% as compared with a mortality of more than double this figure in 25 cases treated concurrently by the conventional methods. They noted a probable shortened course in some instances, a definite improvement in the comfort and in the symptoms of the patients and that in severe cases toxemia was noticeably lessened.

It has seemed to me that all workers heretofore have used very insufficient dosage. Hiss and Zinsser working with rabbits used doses averaging 1/400th of the body weight, and repeated the injections two or three times daily in animals severely sick. The dosage thus far used clinically has been of about 1/6000th body weight or about 15 times too small. I have administered leukocytic extract freely, and it is to this practice that I attribute, rightly or wrongly, the absence of mortality in my series. It is only in the most serious cases that I have resorted to this treatment. It is too expensive and troublesome to use in those patients who are not sufficiently ill to justify extraordinary measures. Given in sufficient dosage I believe that leukocytic extract is our most valuable remedy for lobar pneumonia. Not its least advantage lies in the fact that it is not specific but is of equal value regardless of the nature of the infecting organisms.

My method is as follows: If the leukocytosis is satisfactorily high, I do not administer the leukocytic extract until the third day, or until the patient seems toxic. If the leukocytosis is low or absent I administer it at once and in these cases, and they are usually the severely prostrated ones, the leukocytosis then increases.

The leukocytic extract in salt solution including the cell detritus, is given with a Record syringe, 10 cc. being given at a dose, either under the shoulders or preferably in the skin of the abdomen or outer side of the thigh. A second and third dose is given at three-hour intervals. The temperature usually falls about ten hours after the first dose. The other effects noted are referable to the modification of toxic symptoms, nervousness is allayed, delirium is rarely noted and the degeneration in the kidney is certainly less than one would expect in equally severe cases not so treated. In my nine cases the highest temperature has almost uniformly been before the beginning of the injections, or after they have been interrupted. There is some pain at the site of injection but it is rarely troublesome.

The limitation of time allows only a very short history of the following cases:

Case 1. Josephine W., 5 years old. Ill for four days with fever and prostration before pneumonia developed. Constipation; colon bacilli isolated from blood and urine; stupor marked; pneumonia evident on the fifth day; continuously unconscious for five days; temperature 104°-106° F. Leukocytosis 21,000. Meningismus developed, simulating an extreme meningitis with rigid spine, retraction of head, spastic reflexes, inequality of pupils, and strabismus; spinal puncture showed normal fluid.

Three doses of leukocytic extract each of 10 c.c. were given on the tenth day and again on the twelfth day, none being available on the intervening day. Temperature began to fall, after first three injections, consciousness returned and toxic condition improved. Multiple colon bacillus abscesses developed at the site of hypodermic punctures and double middle ear abscesses occurred. Recovery was complete.

Case 2. Baby S., two years old. Has been since birth a subject of spasmophilia of the type of infantile eclampsia. Lobar pneumonia running for eight days with a temperature from 103° to 106°, pulse from 130 to 160, and severely toxic. Collapse on eighth day. Leukocytic extract, two doses followed in eight hours by a fall in fever and improvement in condition. Temperature rose again the next day and then fell by crisis to normal.

Case 3. Richard B., lawyer, age 35, seen in

consultation with Dr. J. E. Chapin of Redwood City. Had been in Arizona previously for weak lungs. First seen on third day. Temperature 104°, pulse 140 to 160. Sepsis severe. Prostration extreme; cyanosis; thin prune juice-like sputum in large quantities. A leukopenia of 2500 showed the overwhelming character of his infection. An absolutely hopeless prognosis was given the family.

Ten c.c. of leukocytic extract were immediately given and repeated every three hours. The next day he seemed much the same but his white cell count was 10,000. Stimulants, abundant fluid, Ringer's solution subcutaneously, and nourishment constituted the other treatment. The fever and pulse immediately improved. A complicating pleurisy prolonged his convalescence, but after a protracted period of weakness he completely recovered.

Case 4. Mrs. W. H. More than moderately ill with pneumonia. Temperature 103° to 104°. Defervescence not having occurred on the eighth day she received three doses of leukocytic extract. Twenty-four hours later the temperature was normal.

Case 5. Clifford B., 4 years' old. Seen on the third day. Prostration and temperature of 104 2/5°. Pulse 132, respiration 60, and of a grunting type. Complaining of abdominal pain; slight dulness posteriorly and broncho-vesicular breathing. Leukocytosis 21,400. Ten c.c. leukocytic extract given on the evening of the third day and morning of the fourth day. Temperature normal on the fifth day and recovery was prompt.

Case 6. Sam R., 7 years old; patient observed by Dr. Edith Johnson. Seriously ill with bronchopneumonia with temperature from 103° to 104.8°, respiration 40 to 58 and pulse 125. Six doses of Cutter's filtered extract were given on the third and fourth days. Leukocytosis 22,000. Defervescence complete on the seventh day. There was never more than a trace of albumen in the urine, and the toxic condition of the child was scarcely noticeable after the treatment.

Case 7. Mrs. B., age 67. Ill with chill and fever of 103°. The following day temperature of 104°, headache, cough and bloody sputum. Urine heavily albuminous with numerous casts. Coated tongue, stupor and headache, suggested a toxic condition from the complicating nephritis. White cell count 17,500. Consolidation developed slowly, not being evident until the seventh day. Eighth day showed very rapid breathing, delirium, and temperature of 104°. Leukocytic extract begun on the eighth day and repeated at twelve-hour intervals. The fever dropped three degrees in twelve hours from the first dose and was only 99° twelve hours after the third dose. Convalescence uninterrupted.

The seeming results of treatments were: 1. Rapid fall in temperature. 2. Decrease in expectoration and increase in fluidity of sputum. 3. Early disappearance of albuminuria.

Case 8. Edith J., age 32; physician. Taken with severe chill and fever. In 24 hours had pleurisy pain, bloody sputum, severe cough, temperature of 104°, and leukocytosis of 12,000. Consolidation of left lower lobe. A series of five injections of leukocytic extract lowered the fever three degrees. The injections were stopped and the fever rose to 103°. Three more injections were given. The whole right lung became consolidated despite the use of the leukocytic extract. Defervescence occurred on the sixth day. With a severe double pneumonia the patient had no toxic symptoms, had scarcely noticeable albuminuria, defervescence occurred unusually early and an extensive involvement produced noticeably mild toxemia. However, the extract did not precipitate the crisis though begun at the very onset nor was it effective in preventing extension of the disease to neighboring lobes.

Case 9. A. P. B., 35 years. Seen on the second day of his pneumonia. He then had a temperature of 103.8° and a pulse of 140. Was mildly cyanotic. Beginning pneumonia in whole of right lung.

Leukocytic extract of Cutter, the extract of sheep's leukocytes filtered through a Berkfeld filter, was given every four hours in the hope of precipitating a crisis.

The second day the left lung showed signs of involvement posteriorly and the right lung was well advanced toward consolidation. Cyanosis was marked and breathing and cough were labored. Leukocytosis 23,000. On the fourth day the fever was around 99.5° and I was in hope of an early termination but it rose the next day as the lung involvement increased and continued high until the natural crisis on the seventh day.

The noticeable thing about this case was the remarkable mildness of the toxic symptoms as was evidenced by a scarcely noticeable albuminuria, and moderate nervous symptoms and delirium, this in spite of an extensive double pneumonia.

A composite description of these nine cases represents a severe form of pneumonia running a full course with modified temperature curve, scarcely noticeable delirium, comparative freedom from toxic effect on the kidney, and terminating by crisis at the usual time.

From a study of these cases associated with an experience with leukocytic extract in other infections, I have gained the following impressions of its effect:

1. The temperature curve is modified.

2. Leukocytosis is not increased except in overwhelming infections with absence of leukocytosis where the neutralizing effect of the extract relieves the strain on the leukocyte-producing function.

3. Toxic symptoms are noticeably mild.

4. Albuminuria is much less than in untreated cases.

5. The disease is not shortened in its course and extension to neighboring lobes is not prevented.

6. The mortality figures are very remarkably lowered.

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